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REVIEW ARTICLE

Cervical cancer: a tale from HPV infection to PARP inhibitors

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Resistance

Abstract Globally, cervical cancer (CxCa) ranks 4th common cancer among females and led to 569,847 incidences and 311,365 deaths in 2018. 80% of CxCa cases occur due to persistent infection with a high-risk subtype of human papillomavirus (HPV-16 and 18). Smoking, high parity, and co-infection with type 2 herpes simplex or HIV are other known risk factors for CxCa. Major histological subtypes are squamous (70%) and adenocarcinoma (25%). Presently, concurrent radiation plus cisplatin (CDDP)-based chemotherapy is the standard treatment for CxCa patients. However, CDDP resistance and toxic side effects limit its efficacy, leading to a poorer response rate and an expected overall survival ranging from 10 to 17.5 months. Reduced drug uptake, increased DNA damage repair, increased CDDP inactivation, and overexpressed Bcl-2 or caspase inhibition, are primarily accountable mechanisms for CDDP resistance and improving CDDP's efficacy remains the major challenge. Poly (ADP-ribosyl) polymerase-1, an effective mediator of nucleotide excision repair pathway, is involved in DNA repair as well as maintaining genomic stability and is significantly expressed in malignant lymphomas, hepatocellular-, cervical- and colorectal carcinoma, which has been approved effective in maintenance therapy and may serve as an effective target to enhance CDDP sensitivity in CxCa. Here, we summarize the etiology and epidemiology of and treatment for CxCa, the mechanism

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responsible for chemotherapy resistance, PARP inhibitor as a possible therapy for CxCa, and other possible chemotherapeutic options for CxCa treatment.

CxCa and its magnitude

Cervix is the neck of the uterus that acts as a canal connecting the uterus to the vaginal area. An abnormal cellular change often denoted as dysplastic or carcinoma *in situ* (CIN) leads to CxCa; CIN has non-reversible alteration and metastatic potential. Globally, CxCa led to 569,847 incidences and 311,365 deaths in 2018 [1]; approximately 90% of these cases occur in countries with a low socio-economic status.[2] With screening programs and early detection, developed countries have seen a sharp decline in the incidence and mortality of CxCa; however, in developing nations, it remains 2nd commonest cancer accounting for 16.5% of total gynecological cancer[1,3] and 10% of gynecological cancer-related mortality.[3] Western and Eastern Africa record the highest incidence rates for CxCa, followed by Southern Africa, South-Central Asia, South America, and Middle Africa respectively. North America, followed by Western Asia and Australia/New Zealand, record the lowest incidence rates.[4,5]

CxCa: etiology

Over 100 HPV types have been identified and classified into five major genera referred to as alpha-, beta-, gamma-, delta-, and mu-papillomaviruses.[6,7] Of these, high-risk subtypes are key players for CxCa, while low-risk subtypes generally do not cause any diseases; however, a few may lead to warts at the genital region or the throat or around the mouth, or in rare cases, benign tumor inside the respiratory tract.[7]

HPVs belong to the family *Papillomaviridae*, have a genome size of 6.8—8.0 kbp and encode six early (E) proteins, namely E1, E2, E4, E5, E6 and E7, and two late (L) proteins, namely L1 and L2 (Fig. 1A).[8] E1 and E2 regulate DNA replication and translation; E4 regulates cytoskeleton reorganization. E2 also acts as a transcriptional repressor of E6 and E7. E5, along with E6 and E7, regulate the cell transformation, whereas L1 and L2 form minor and major capsid proteins and therefore structure of the virus, respectively.[6] Life cycle of HPV is dependent upon the basal layer of epidermal or mucosal epithelial cells capable of proliferation (Fig. 1B).[8] Upon infection with HPV, its DNA integrates into the host DNA leading to the disruption of E2 gene. Loss of E2 protein removes repression on E6 and E7 protein leading to their increased level, thereby causing genomic instability and disruption of the host's cell cycle.[6,9] The HPV-infected cells undergo multiple rounds of cell divisions; along with lateral HPV spread through E4 protein. Inside the host epithelial cell, E6 binds to p53 protein and results in its degradation and loss of its tumor suppressor activity. Whereas E7 protein binds to pRb protein of the host cell, causing the release of E2F, which is a DNA replication-promoting transcription factor.[6,9]

HPV infection and vaccines of choice

Since HPV infection is a central requirement for CxCa, preventing HPV infection can prevent the occurrence of CxCa. Three such vaccines are available and they are based on targeting the L1 and L2 proteins of HPV (Table 1B).

CxCa: histology

Squamous cell carcinoma and adenocarcinoma are two major histological types of CxCa and account for 70% and 25% of all CxCa cases respectively.[10]

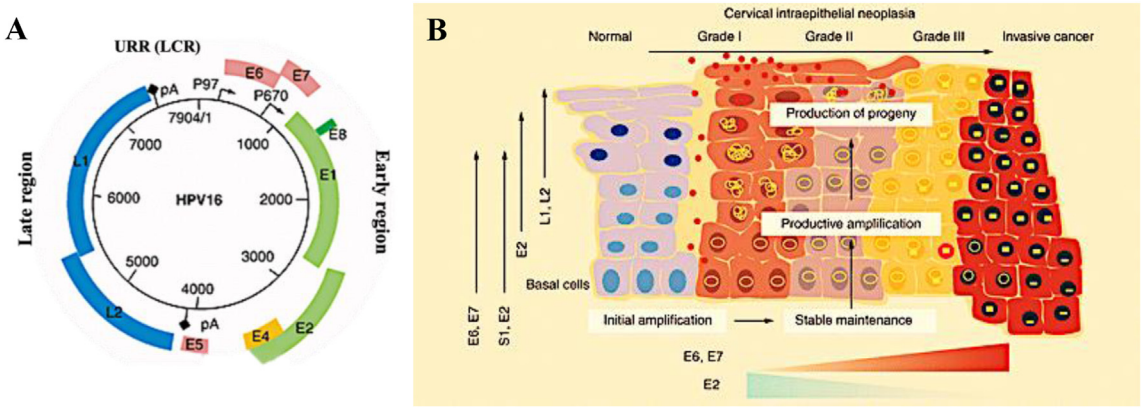

Figure 1 Genome and the pathogenic cycle of HPV. **(A)** Schematic view of HPV16 circular dsDNA genome. **(B)** The life cycle of HPV in association with cancer development. Reproduced with modifications from *Future Virology. 2016;11(2)*:141—155.[8]

Table 1 HPV categorization as per its carcinogenic potential **(A)** and HPV types targeted by HPV vaccines **(B)**.

High-risk HPV		HPV types
A		
	Carcinogenic	16,18,31,33,35,39,45,51, 52,56,58,59
	Probably carcinogenic	68
	Possibly carcinogenic	26,53,66,67,70,73,82
	Tested in commercially available detection systems	16,18,31,33,35,45,51,52, 56,58,59,66,68
Low-risk HPV		6,11,40,42,43,44,54,61,72,81,89

Name	Company	Protection against	Approved by/usage	Nature of vaccine & efficacy against infection	Route for administration /Schedule	References
B						
Cervarix	Glaxo Smith Kline	HPV 16 and 18; CIN I, CIN II, cervical adenocarcinoma *in situ*.	FDA in 2009 for females aged 9—25 years old	Bivalent/9 years	3 doses of intramuscular injection, 0.5 mL each on months 0, 1 and 6	[a,83,84]
Gardasil	Merck	HPV 6, 11, 16, and 18; cervical, vaginal, and vulvar cancers, precancerous lesions, genital wart, CIN II, and CIN III	FDA in 2006 for females aged 9—25 years old	Quadrivalent/ 10 years	3 doses of intramuscular injection, 0.5 mL (20, 40, 40, 20 μg of VLPs) each on months 0, 1 and 6	[85—89]
Gardasil 9	Merck	HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58; approximately 90% of cervical, vaginal, vulvar, and anal cancers; genital warts	FDA in 2014 for females aged 9—26 years old and males aged 9—15 years old	9-valent/6 years	3 doses of intramuscular injection, 0.5 mL each on months 0, 2 and 6	[90—92]

[a] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProduct.
Source: American Journal of Obstetrics and Gynecology, vol. 208, no. 3, 2013, pp. 169—75.

Squamous cell carcinoma and its pathogenesis

Squamous cell carcinoma or epidermoid carcinoma develops from cervical intra-epithelial neoplasia (CIN). CIN is a usual health issue among females of reproductive age. Based on their degree of proliferation, CIN can be categorized into three grades, CIN1, CIN2, and CIN3, which are referred to mild, moderate, and severe dysplasia respectively.[11] A recent approach based on the Bethesda system for cervical cytology distinguishes CxCa between two categories, low- and high-grade squamous intraepithelial lesions (LSIL and HSIL respectively). LSIL is associated with low-/intermediate-risk HPV type; viral DNA remains as an episome and the cells show extensive HPV-related cytological changes like koilocytosis and proliferation of the basal as well as mild atypical parabasal cells with mitosis. Whereas HSIL harbors High-risk HPV DNA integrated into the host genome[12] and is characterized by small-to medium-sized atypical basal cells that might involve the whole thickness of the epithelium and frequently lack visible HPV-related cytological changes.

Adenocarcinoma and its pathogenesis

Adenocarcinoma *in situ* (AIS), a premalignant precursor to adenocarcinoma, is manifested by reactive alterations of the glandular endocervical epithelium and tubal metaplasia. It is also characterized by cellular atypia showing a variety of cellular differentiation including goblet cells. Nuclei of the infected cell become cigar-shaped and pseudostratified, with coarse chromatin and numerous mitoses. The precursor of AIS is considered to be glandular dysplasia.[13,14] Besides, adenosquamous carcinoma is a rare type of CxCa and include tumor with both squamous and glandular differentiation and accounts for 5%—20% of total CxCa cases.[15] Other rare CxCa types include adenoid-basal carcinoma and neuroendocrine carcinoma.

CxCa and its treatment

CxCa treatment relies on the International Federation of Gynaecology and Obstetrics (FIGO) staging system. Commonly, for FIGO stage IA2 to IB1 and certain stage 2A cases, surgery with radical hysterectomy and pelvic lymphadenopathy is the optional treatment.[16] Radiation therapy is generally used for early stage i.e., IB1 and IIA with tumor size less than 4 cm. For tumors with a size of more than 4 cm, radiation plus chemotherapy, is used. The addition of CDDP in chemoradiation not only improves patients' survival but also reduces the risk of cancer recurrence.[16] Radiotherapy uses ionizing rays that work by targeting DNA damage in cancerous cells thereby causing cellular death. Likewise, radiation beams are focally directed on several angles to intersect the tumor, therefore providing a much larger adsorbed dose the at tumor than the surrounding healthy tissue. They are normally delivered by linear accelerators either given as an external beam or through internal radiation (known as brachytherapy). The majority of female patients with CxCa are treated with surgery, and

however, may be administered with chemotherapy before (neo-adjuvant) or even after surgery (adjuvant). Chemotherapy is basically used to treat patients with locally advanced CxCa and as a palliative treatment for CxCa in the metastatic stage.[17,18] First-line chemotherapy for CxCa patients comprises paclitaxel and CDDP. Other chemotherapy drugs used are carboplatin and topotecan. Chemotherapy is often used as concurrent chemoradiotherapy and can be combined with newer targeted drugs like bevacizumab.[18] Currently numerous targeted therapeutic agents are under clinical trials, some of these are based on inhibiting angiogenesis or cyclooxygenase 2, and targeting histone deacetylases or EGFR, which present hope for better and precise CxCa chemotherapeutic agents.[18]

CDDP: cornerstone CxCa treatment

CDDP or cis-$[Pt(NH_3)_2Cl_2]$ is a neutral inorganic, square planar coordination complex and exists in two isomers, cis and trans -forms. CDDP has been approved for its treatment of testicular and ovarian cancer by U.S. FDA on 19 December 1978[19] and the UK in 1979[20] and served as a breakthrough in the development of efficacious cancer chemotherapeutic agents. CDDP interacts with DNA and forms CDDP-DNA adducts, leading to cancer cell death.[21] To date, it is the most active agent against CxCa and is used in primary treatment in weekly doses of 40 mg/m^2 along with radiation over 6 weeks (concurrent chemoradiation). For patients with recurrent or metastatic CxCa, CDDP is used either as a single agent or in combination with paclitaxel.[16]

CDDP needs to be activated, and inside cells, it spontaneously undergoes an aquation process and displaces its one chloride ion by water molecule making an aqua complex, *cis*-$[PtCl(NH_3)_2(H_2O)]^+$; extremely low concentration of chloride ions (3—20 mM) inside the cells compared to extracellular fluid (100 mM) highly favors the CDDP aquation,[22] and the added water moiety is then easily displaced by the *N*-heterocyclic bases on DNA thereby allowing CDDP binding to DNA (Fig. 2A).[23,24]

Guanine is favored for crosslinking with CDDP over adenine and crosslinking occurs via displacement of the other chloride, majorly by another guanine base, along with a linear correlation corresponding to the level of platinum bound to DNA and the extent of CDDP cytotoxicity (Fig. 2A).[24,25] Damaged DNA initiate DNA repair mechanisms leading to either repair of DNA breaks and cell survival or activation of irreversible apoptotic signaling in case DNA damage repair upholds impossible.[25] Besides, mitochondrial DNA (mtDNA) is a potent target of CDDP and its rich guanine residue stretch (in contrast with nuclear DNA) brings about higher CDDP-mtDNA adducts and thus serves more vulnerable due to low DNA repair ability.[26]

CDDP: DNA damage and recognition

CDDP-induced cytotoxicity is summarized in Figure 2B.[27] CDDP-DNA adducts cause DNA bending, which is recognized by several proteins like the high mobility group (HMG) protein; HMG1 binding shields CDDP-DNA adducts from repair mechanisms. HMG binding diminishes the efficiency of NER (nucleotide excision repair) and MMR (mismatch repair) pathways and therefore, diminishes DNA damage repair.[28] At the cellular level, CDDP administration generates extensive super anions and hydroxyl radicals which damage cellular proteins, lipids (membranes), as well as DNA and thereby temper cell survival signaling.[29] Generation of ROS severely damages mtDNA due to its nucleosome-free structure, followed by more vulnerable DNA plus limited DNA repair ability.[26] At the cellular level, CDDP-DNA adducts lead to temporary cell cycle arrest that allows recognition and safe removal of these adducts by DNA repair pathways. G1/S and G2/M transitions are the two main checkpoints; the G1/S checkpoint allows DNA restoration before DNA synthesis and the G2/M checkpoint allows repair of damage that occurs during the S and G2 phase; both checkpoints prevent the segregation of damaged DNA into daughter cells. CDDP causes G2 arrest by phosphorylating checkpoint kinases Chk1 and Chk2, activation of Cdc25C, and its translocation to the cytoplasm, which induce cell cycle arrest in the G2 phase.[30]

Cell cycle arrest is crucial to allow the NER complex to eliminate adducts and promote the cell's survival. So, the repair is intimated to checkpoint activation and apoptosis; it is noteworthy that all three processes are collectively associated with p53 protein.[31] p53 protein plays a central role in chemotherapy-induced apoptosis. p53 prompts apoptosis via transcriptional activation of pro-apoptotic genes including PUMA, caspases, PIDD, MAPK family, and repression of anti-apoptotic genes, therefore, activating apoptosis via multiple pathways.[25] p53 also activates p21/waf1, mdm2, and GADD45 that result in cell cycle arrest and activation of DNA repair pathway.[32] p53 also regulates CDDP-mediated apoptosis by interacting with Bcl 2 family proteins in mitochondria and/or cytosol and hence the intrinsic pathway.[33] CDDP activates the ATR kinase and ATR and then phosphorylates p53 on serine-15, resulting in activation of p53.[34] However, in case of irreparable DNA damage, the cell activates apoptotic mechanism and prevents cellular passage into mitosis. CDDP-mediated DNA damage causes apoptosis through the intrinsic pathway in which the Bcl2 family proteins regulate apoptosis through cytochrome c (involving apoptotic protease activating factor-1 and caspases 9 and 3). Though various treatment strategies are available for CxCa, CDDP-based concurrent chemoradiotherapy remains the major treatment strategy. Although the patient's initial responsiveness to treatment is high, the development of primary and secondary resistance limits its clinical efficiency.[35]

CDDP: development of resistance

Though CDDP acts as a keystone for CxCa treatment, CDDP resistance and its toxic side effects limit its efficacy and lead to the overall survival of 10—17.5 months.[21,36] Resistance to CDDP can be acquired through chronic drug exposure or present as an intrinsic phenomenon; at least two-fold CDDP resistance has been determined in clinical studies.[37] However, 50- to 100-fold higher resistance has been observed in *in vitro* studies using CxCa cell lines derived from clinically refractory tumors compared to those from sensitive tumors with the same cytotoxic

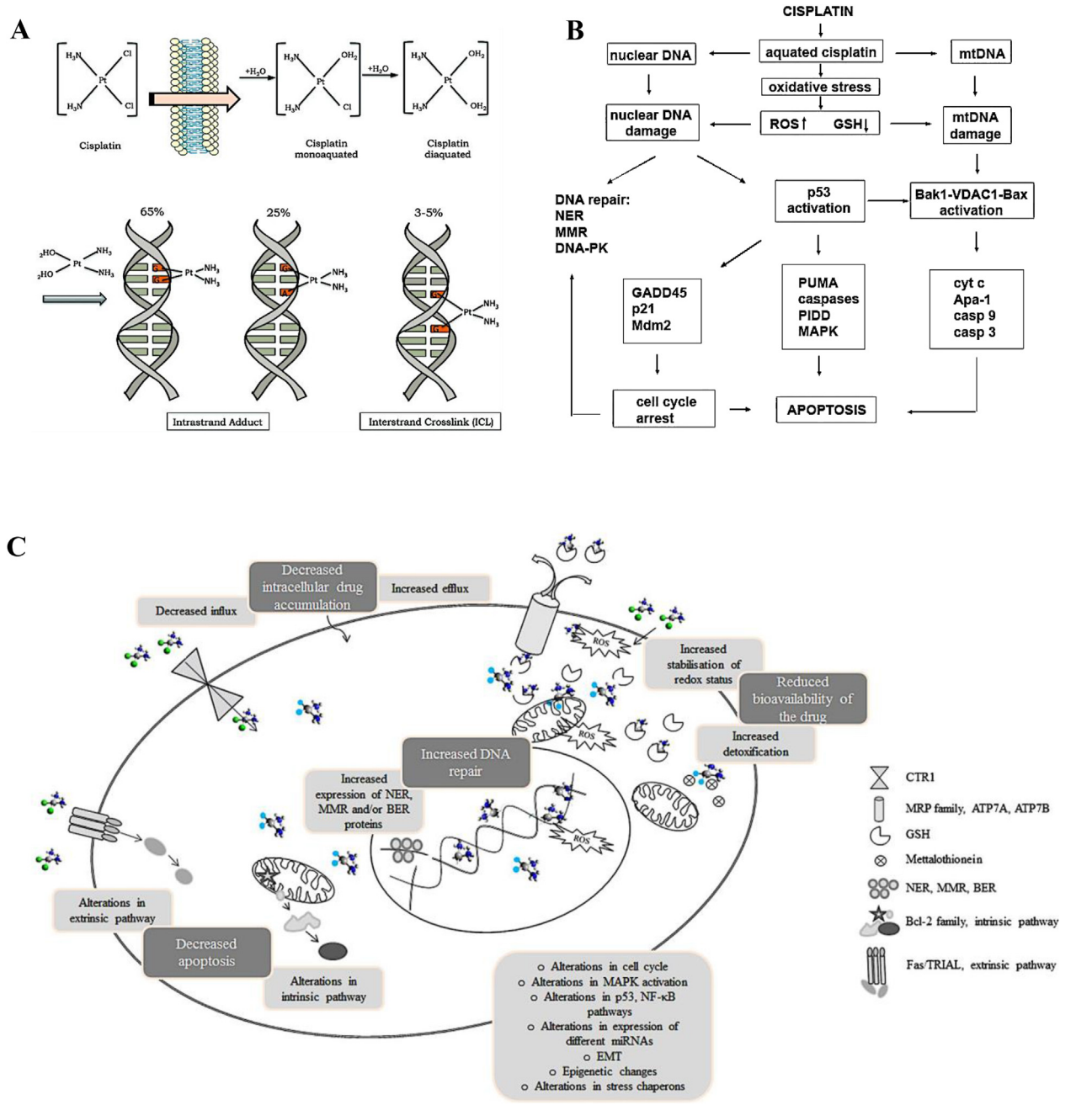

Figure 2 Schemata for CDDP activity and resistance development. **(A)** CDDP activation and DNA damage induction. **(B)** Molecular mechanism of CDDP toxicity. **(C)** Molecular mechanisms responsible for CDDP resistance. Reproduced with modifications from *Clinics (Sao Paulo)*.2018; 73(suppl 1):e478s[24]; *Medicine and Biology*.2016; 18(1):12—18 [27]; *Archives of Toxicology*. 2017; 91(2):605—619.[40]

effect.[38] Drug resistance is a multi-factorial process, with multiple mechanisms acting simultaneously within the same tumor cells (Fig. 2C).[39,40]

Reduction in drug accumulation inside the cells accounts for 70%—90% of total resistance and is a prominent cause of CDDP resistance. Cell lines with 3—40 folds of CDDP resistance accumulate 20%—70% less CDDP as compared to sensitive cells.[39] Reduced CDDP accumulation can be due to decreased drug uptake or increased drug efflux and even both; reduced CDDP uptake appears prevalent.[32,36] ATP-binding cassette (ABC) transporters, including multidrug resistance proteins (MRPs), induce CDDP resistance by increasing CDDP export. Overexpression of MRP1 is associated with CDDP resistance in some CxCa cells[41]; similarly, MRP2 contributes to higher CDDP efflux in CDDP-resistant human hepatic cancer cells and melanoma cells.[42,43] P-glycoprotein P-gp, another ABC transporter, mediates the efflux of CDDP conjugates and therefore stimulates CDDP resistance. P-gp is highly expressed in SiHaR, a CDDP-resistant cell line[41]; similarly, its expression is rapidly enhanced upon CDDP exposure in HeLa cells.[44]

Another reason behind reduced CDDP accumulation i.e., reduced CDDP uptake has also been reported in CDDP-

resistant CxCa cells. The CDDP-resistant HeLa cells[45] and A431 (A431/Pt) cells[46] respectively have shown up to 50% and 77% reduction in CDDP uptake compared with their parental cell lines.[44] Ishida et al found that the level of DNA-CDDP adducts, in the various organs in a CxCa mouse model, was proportionate to CTR1 mRNA level, indicating that CTR1 may regulate CDDP uptake *in vivo*.[47] Alterations in the non-saturable process of passive drug diffusion and active transport involving the sodium pump Na^+/K^+-ATPase or a gated ion channel, play roles in CDDP uptake.[48] Up to 10-fold increased multidrug resistance-associated 2 (MRP2), and raised ATP7A and ATP7B (copper-transporting P-type ATPase) levels are found in resistant tumors.[42]

Mono-aquated form of CDDP is highly susceptible to nucleophiles like GSH and metallothionein, which could decrease the amount of drug available for the formation of DNA adducts. Increased GSH has been determined both in tumor models and clinical studies.[49] Metallothionines are thiol-rich cysteine molecules and about 5-fold levels in CDDP-resistant murine and human tumor models were found.[50] Stabilization as well as activation of wild-type p53 is a crucial step for CDDP-mediated cell death. Therefore, cancer cells having a defect in p53 functioning fails to activate the cell death program, a feature characteristic of resistance development due to disrupted signal transduction inside the cell.[39] Besides mutation in p53, other intracellular factors like $p14^{ARF}$, the negative feedback regulator of mdm2 and downregulation moderator of mdm2, may inhibit p53 activation.[51] E6 protein in HPV-16 binds to p53 and disrupts its transactivation and apoptotic function thus leading to platinum resistance.

MAPK sub-family members, namely p38, JNK, and ERK, are closely associated with CDDP activity. Upon activation, the Ras/MAPK pathway leads to post-translational modification of p53 and also activation of other transcription factors like c-Myc, c-Fos, and c-Jun. Besides, the c-Fos/c-Jun heterodimeric complex AP1 (activator protein-1) induces ERCC1 (excision repair cross-complementation group 1), metallothionein, and glutathione-S-transferase, and mediates increased DNA damage repair and drug inactivation leading to CDDP resistance.[52]

Persistent formation of CDDP-DNA adducts is vital for cell apoptosis. Enhanced repair results in 1.5-to-2-fold resistance, though little but still significant as CDDP primarily acts by forming DNA adducts.[38] Of all the repair pathways, NER is considered majorly responsible for DNA damage repair.[53] A 2-fold increase in the ERCC1 mRNA level has been observed in CDDP non-responders.[48,54] Also, hyperactivation of PARP-1 (Poly (ADP-ribosyl) polymerase-1), a nuclear DNA binding protein and a key component of the NER pathway, often develop CDDP resistance.[55]

PARP-1: the new target

PARP-1 is the first identified and best-studied protein of the PARP family, which consists of 18 distinct enzymes. PARP-1 is a highly conserved, multifunctional enzyme. Structurally it comprises three functional domains, namely the amino-terminal DNA-binding domain (DBD) required for PARP-1 binding to single-strand breaks (SSBs) and double-strand breaks (DSBs), the auto-modification domain, and the COOH-terminal catalytic domain.[56,57] The third domain is present at the carboxy-terminal and the highly conserved catalytic domain, which consecutively transfers ADP-ribose moieties derived from ADP donor NAD^+ leading to the liner or branched PAR polymers at the target proteins as well as itself.[58] Following 15—30 s of SSBs or DSBs, PARP-1 is promptly recruited to the damage site through its DNA binding domain and results in 10- to 500-fold increased activity. Through its PARylation activity, PARP-1 adds multiple units of ADP-ribose through 2',1"-O-glycosidic ribose—ribose bonds to generate long linear (approximately 200 ADP-ribose units) PAR chains branched every 20—50 ADP-ribose units (Fig. 3A).[59,60] These PAR moieties are added to Glu, Asp or Lys residue of acceptor proteins via trans-esterification reaction[50]; components of the DNA damage repair pathway, histones, topoisomerase I and DNA protein kinase (DNA-PK) are acceptor proteins.[61,62] Added PAR chains also recruit other proteins like XRCC1, the scaffolding protein that assembles and activates the DNA NER machinery[63,64] to bind directly to PAR, whereas other proteins are indirectly recruited by interacting with PAR-binding proteins. Negatively charged and heavy PAR chains decrease the affinity of histones to DNA resulting in local modification of chromatin compaction (Fig. 3A and B).[60,65,66] PARP-1 has also been found associated with HPV infection and CxCa development. PARP-1 expression is significantly associated with HPV positivity in high-grade squamous intraepithelial lesions.[67] PARP-1-/- mice are highly vulnerable to carcinogenesis upon treatment with alkylating agents.[68] Further, small nucleotide polymorphism in PARP-1, particularly PARP-1 Val762Ala (GTG/GCG), is considerably associated with increased susceptibility to carcinogenesis in the prostate, esophageal squamous cell carcinoma, smoking-related lung, and gastric cardia cancer.[69,70] Ala762Ala(GCG/GCG) SNP in PARP-1 is associated with an increased risk of CIN and hence, the development of cervical carcinoma.[70]

PARP-1 inhibitors in chemotherapy

PARP-1 is involved in DNA damage repair and cell proliferation, hence survival and cell apoptosis and its expression are enhanced in numerous tumors. Therefore, it serves as an attractive anticancer therapeutic target in preclinical research and clinical trials.[71] Use of PARP-1 inhibitors is based on the concept of synthetic lethality, a condition where if two different gene aberrations co-occur, it is lethal, however, if only one of them is mutated, the cell survives. Hence, PARP inhibitor leads to cell lethality in cancer cells already mutated with genes critical for performing homologous recombination repair like BRCA1/2.[72] The combination of two genetic events i.e., loss of double-stranded break repair and use of PARP inhibitor that blocks repair of single-stranded break leads to cell death and hence tumor with BRCAness is sensitive to PARP inhibitors.[72,73]

The initial discovered PARP-1 inhibitors contained derivatives of nicotinamide/benzamide. Nicotinamide is the catabolite of NAD^+ in the PARP-1-dependent DNA repair pathway and acts as a structural model for PARP-1 inhibitors. Benzamide ring is crucial for the functioning of PARP-1 inhibitors since it holds nicotinamide in the plane

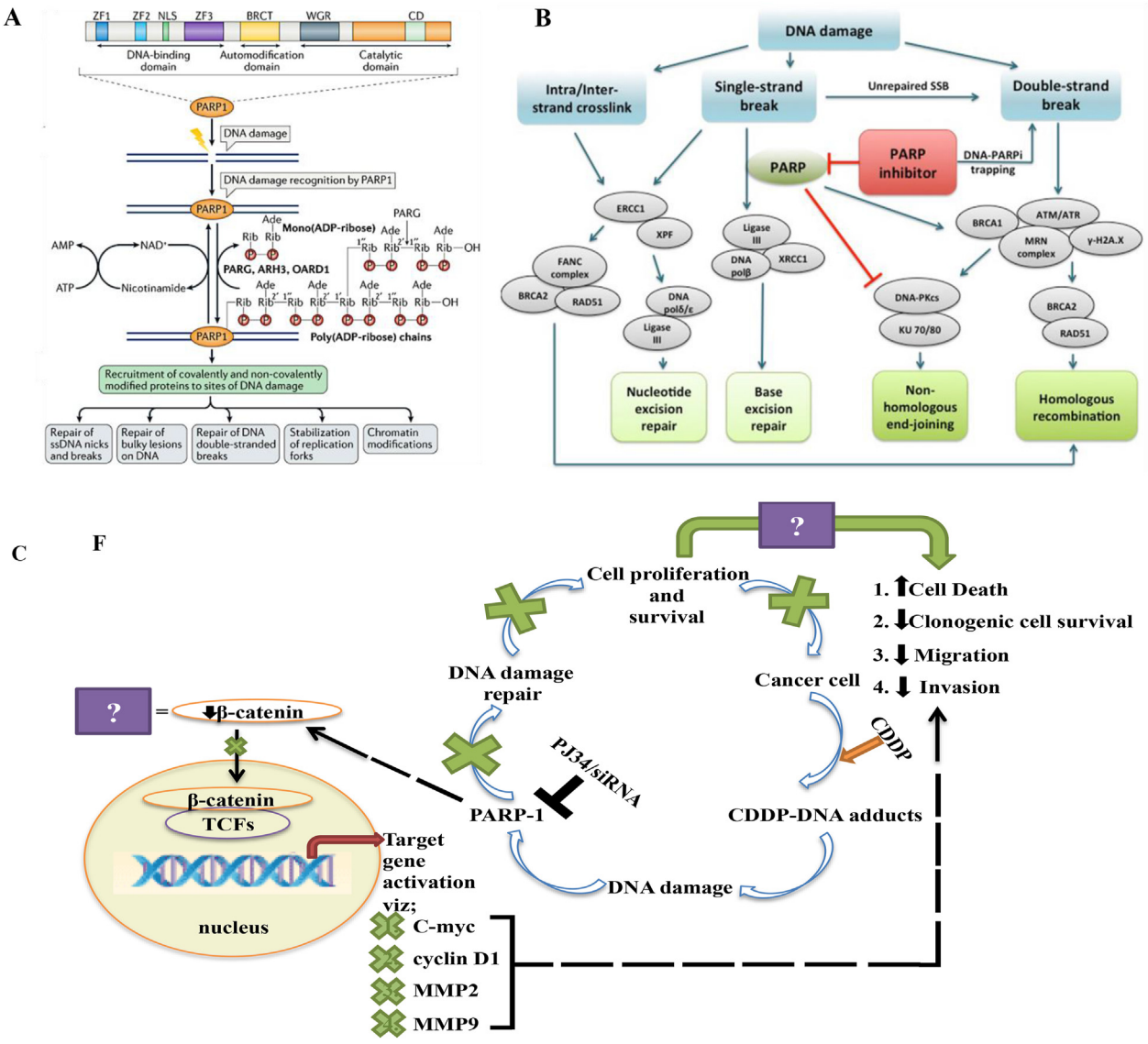

Figure 3 The role of PARP-1 in DNA damage repair pathways. **(A)** The biochemical function of PARP-1 in DNA damage repair. **(B)** Schemata showing PARP-1 participation in DNA damage repair network. **(C)** Model for PARP-1 regulating β-catenin signaling to cause cell death, decreased cell metastasis, and thereby, augmenting CDDP sensitivity. Reproduced with modifications from *Nature Reviews Molecular Cell Biology.2017;* 18(10):610–621 [60]; *Frontiers in Oncology.2014;4:42* [66]; *Oncotarget.2019;* 10(42):4262–4275.[78]

of the benzene ring. Nicotinamide/benzamide-mimic pharmacophores are characteristic structural basis for exploring as well as designing PARP-1 inhibitors. Currently, all presently available PARP-1 inhibitors under clinical trials carry nicotinamide-mimic motifs to inhibit PARP-1/NAD $^{+}$ interaction by competing with the nicotinamide.[74] Olaparib, niraparib, rucaparib, talazoparib, and veliparib are FDA-approved PARP-1 inhibitor drugs for BRCA mutated cancers such as breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer (Table 2A).

PARP inhibitors and CxCa

There is limited evidence on the efficacy of PARP inhibitors either alone or in combination with cytotoxic drugs in HPV-associated CxCa; the majority of studies involve preclinical data. Bianchi *et al.* found that 3 out of 9 CxCa cell lines showed high PARP activity and were highly sensitive to olaparib.[75] Upon CDDP treatment CxCa cells showed significantly higher PARP-1 expression and the use of olaparib led to significantly decreased cell survival and proliferation and delayed γH2A.X foci.[76] Similarly, rucaparib also has a significant anti-proliferative effect; it causes G2/M arrest, reduces cyclin D1 and CDK4 expression, and suppresses cancer growth *in vivo* and *in vitro*. Besides, rucaparib enhances radiation sensitivity.[77] In our previous study, we found that PJ34, a phenanthridinone-derived small molecule inhibitor of PARP-1, enhances CDDP sensitivity in CxCa cell lines by down-regulating WNT signaling and significantly decreasing cell proliferation, survival, apoptosis, invasion, and migration (Fig. 3C).[78] Furthermore, compared to β-catenin inhibition, PARP-1 inhibition served better to synergies the CDDP-

Table 2 Characteristics of PARP-1 inhibitors approved for cancer treatment **(A)**, PARP inhibitors in CxCa **(B)**, and ongoing trials for PARP inhibitors in CxCa **(C)**.

Drug Name	Manufacturer	Administration route	Tumor targeted	Trial status	IC_{50}/K_i value (nM)	References
A						
Veliparib ABT-888	Abbott	Oral	Brest, ovarian, primary peritoneal, fallopian tube, colon, prostate, melanoma, CNS, multiple myeloma HCC, hematologic malignancies/CLL, lymphoma, and advanced solid tumors	I/II single or combination	IC50: n/a; Ki: PARP-1: 5.2, PARP-2: 2.9	93,94
Olaparib Lynparza AZD2281	AstraZeneca	Oral	Triple-negative breast, BRCA-associated breast/ovarian, ovarian, gastric, colon, prostate, advanced solid tumors	I/II single or combination	IC50: PARP-1: 5, PARP-2: 1; Ki: n/a	93,94
Iniparib BSI-201 SAR240550	BiPar Sciences/ Sanofi-aventis	IV	Triple-negative breast, BRCA-associated breast/ovarian/ pancreas, ovarian, primary peritoneal fallopian tube, uterine carcinosarcoma, glioblastomamultiforme, NSCLC, squamous cell lung cancer	I, II, III		94
Rucaparib CO-338	Clovis	IV and oral	Breast, ovarian, solid tumors, and diabetes mellitus	I: combined with chemotherapy; II: singly in BRCA-associated status	IC50: PARP-1:0. 8, PARP-2: 0.5; Ki: PARP-1: 1.4, PARP-2: n/a	93
Niraparib MK-4827	Tesaro	Oral	Recurrent epithelial, ovarian, fallopian tube, primary peritoneal cancer with complete/partial response	II: ovarian; III: breast, ovarian	IC50: PARP-1: 3.8, PARP-2: 2.1; Ki: n/a	93,95,96
Talazoparib MK-673	Pfizer	Oral	Locally advanced or metastatic breast cancer with gBRCAmut status	II: breast, ovarian, endometrial, advanced tumors; III: breast, ovarian	IC50: PARP-1: 0.57, PARP-2: n/a; Ki: PARP-1: 1.2, PARP-2: 0.85	95,96

Trial name	Treatment strategy	Patients enrolled	Phase	Treatment	Overall survival	Progression-free survival
B						
NCT#01281852	Paclitaxel, cisplatin, and veliparib in treating patients with advanced, persistent, or	Persistent or recurrent CxCa	I	Dose-escalation study. Paclitaxel 175 mg/m2 on day 1, cisplatin 50 mg/m2 on day 2, and escalating doses of veliparib ranging from 50	14.5	6.2

	recurrent CxCa			to 400 mg administered orally twice daily on days 1–7		
NCT#737664	Veliparib, topotecan hydrochloride, and filgrastim or pegfilgrastim in treating patients with persistent or recurrent CxCa	Pretreated persistent or recurrent CxCa	I–II	Single-arm study. Veliparib 10 mg administered orally twice daily on days 1–5 with topotecan 0.6 mg/m^2 administered IV once daily on days 1–5 of each cycle	8	2

Trial name	Patients enrolled	Phase	Treatment	Status
C				
NCT03476798	Recurrent CxCa	II	Rucaparib in combination with Bevacizumab	Ongoing
NCT03644342	Metastatic invasive CxCa	I/II	Niraparib in combination with radiotherapy	Ongoing

mediated cytotoxicity in both CxCa cell lines. β-catenin inhibition enhanced PARP-1 expression resulting in decreased cell sensitivity compared to PARP-1 inhibitor plus CDDP.[79] However, the data is from *in-vitro* experiments. Clinically, few studies to date have explored the efficacy of PARP inhibitors in CxCa. A phase I trial of combinatorial treatment with veliparib and CDDP and paclitaxel showed well tolerance as well as encouraging results in both persistent and recurrent CxCa.[80] Table 2B and C list the clinical trials on PARP inhibitors in CxCa.[81] Besides combination with chemo/radio-therapy, PARP inhibitors are also under investigation with immunotherapy; combinatorial therapy of bevacizumab with rucaparib is also under phase II trial (Clovis-001; NCT03476798) in recurrent CxCa patients. Studies have also shown that PARP inhibitors induce immunogenic cell death and lead to increased tumor neoantigens and upregulated interferons and programmed death ligand 1 (PD-L1), and also, modulate tumor microenvironment leading to intense anti-tumor immune response.[82]

Conclusion

With the first PARP inhibitor, olaparib, being approved the for treatment of gBRCA-mutated cancer in 2014, to date there is no clinical trial evaluating the PARP inhibitors in CxCa, data hence available is more robust for ovarian cancer. For CxCa data thus far available is more of preclinical and early trials but shows promising results. New insights into the mechanism responsible for the cytotoxic effect of PARP inhibitors, the pathogenesis of diseases, and the identification of prognostic markers will further help to define the cohort that would be maximally benefitted.

Conflict of interest

The authors declare no conflict of interests.

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